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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,777	04/09/2004	Winston T.K. Cheng	682821-4US	8832

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,777	CHENG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,23-34 and 37* is/are pending in the application.

4a) Of the above claim(s) *32-34 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 23-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-27-08 has been entered.

Claims 1-18, 20-22, 35 and 36 have been canceled. Claim 37 has been added. Claims 19, 23-34 and 37 are pending.

Applicant's arguments filed 12-26-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 32-34 submitted 6-29-07 remain and new claim 37 submitted 8-27-08 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The milk (claims 32-34 and 37) is patentably distinct from the transgenic and method of making the transgenic. Inventions are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product,

and the species are patentably distinct (MPEP § 806.05(j)). In the instant case, the intermediate product (transgenic) is deemed to be useful as food and the inventions are deemed patentably distinct because there is nothing on this record to show them to be obvious variants. Claims 32-34 do not clearly set forth the milk collected has the FVIII protein.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-34 remain withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 19 and 23-31 remain under consideration as they relate to transgenics and methods of making transgenics.

Claim Rejections - 35 USC § 112

The rejection regarding the phrase "up to about 50 mg" (claim 27) has been withdrawn in view of the amendment.

Claims 19, 23-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not support a B-domain deleted human clotting factor VII having a recombinant spliced site, Ser 741 link to Leu 1643. Support has not been provided by applicants and none can be found in the specification as originally filed.

While not under consideration, it is noted that pg 25 and original claim 16 do not support milk having up to 50 mg of the B-domain deleted human FVIII polypeptide/liter of milk as in claim 37. Pg 25 discusses concentrations of human rFVIII, not B-domain deleted hFVIII.

Indefiniteness

The rejection of claim 27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of the amendment.

Claims 19 and 23-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "a B-domain deleted human clotting factor VII having a recombinant spliced site, Ser 741 link to Leu 1643" cannot be determined. The phrase "spliced site, Ser 741 link to Leu 1643" does not make sense and does not clearly set forth the structure of the protein or the splice site(s). The nomenclature used by applicants does not explicitly or implicitly set forth the structure of the protein or the splice site(s). Clarification is required.

Rejections - 35 USC § 103

Claims 19 and 24-31 remain under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

Chen made a transgenic mouse comprising a vector encoding 7.2 kb of hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid bovine a-LA signal peptide sequence (pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13 and encoded by SEQ ID NO: 1. Claim 19 only requires the claim only requires “a" peptide of SEQ ID NO: 14, which can be interpreted broadly. The signal peptide used by Chen meets the limitation because it contains at least one bovine α-S1 casein signal peptide of SEQ ID NO: 14. The mouse was made by introducing the transgene construct (i.e. expression cassette) into an embryo, implanting the embryo into a recipient female, allowing the embryo to develop to term, and testing the resulting offspring and identifying mice that secreted hFVIII in milk by RT-PCR and analysis of the milk for protein (paragraph bridging columns 1 and 2 of pg 263). Chen did not delete the B-domain of hFVIII.

However, Soukharev suggested making transgenic mammals expressing B-domain deleted FVIII to improve yield of FVIII (pg 241, paragraph bridging columns 1 and 2). “[A]nother approach to improve recombinant FVIII molecule is to introduce modifications to improve its effective secretion from FVIII-expressing cell" (page 239, col. 1, paragraph 1, lines 1-4) and that “removal of the B domain...was found to

dramatically improve the yield of FVIII" (page 237, col. 2, lines 3-6). Soukharev taught "an attractive possibility to increase the yield of rFVIII is to produce a biologically active form of FVIII by coexpressing its heavy and light chains" (page 239, paragraph 2, line 1 to col. 2, line 2). The phrase "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" encompasses any B-domain deleted hFVIII protein of SEQ ID NO: 15. The nucleic acid sequence encoding the B-domain deleted hFVIII taught by Soukharev encodes "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" as in claim 24. Without evidence to the contrary, the B-domain deleted hFVIII taught by Soukharev inherently produces a hFVIII comprising a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) operably linked by a junction as in claim 25.

Thus, it was obvious to those of ordinary skill in the art at the time of filing to make a transgenic mouse encoding hFVIII as taught by Chen, wherein the hFVIII had a deletion in the B-domain as taught by Soukharev. Soukharev provides motivation on pg 241, lines 1-5. Those of skill would have a reasonable expectation of successfully improving the yield of FVIII as suggested by Soukharev because results in vitro improved the yield (pg 237, "Genetic engineering to improve the yield of recombinant FVIII). Lubon provides further evidence that fragments of hFVIII could be made in a non-human transgenic animal (claim 1 of Lubon).

The phrase "recombinant spliced site, Ser 741 link to Leu 1643" is included because the metes and bounds of the structure claimed cannot be determined.

Claim 27 is included because "producing up to 50 mg" per liter encompasses expressing any amount up to 50 mg/l (µg/ml) and because Chen taught an average

concentration of hFVIII of 20 µg/ml. The phrase "up to 50" µg/ml encompasses 20 µg/ml taught by Chen. Claim 27 is also included because Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "up to 50 µg/ml" as claimed.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 19 and 23-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and DeBoer (US Patent 5,633,076, Issued May 27, 1997) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

Chen made a transgenic mouse comprising a vector encoding 7.2 kb of hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid bovine a-LA signal peptide sequence (pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13 and encoded by SEQ ID NO: 1. The mouse was made by introducing the transgene construct (i.e. expression cassette) into an embryo, implanting the embryo into a recipient female, allowing the embryo to develop to term, and testing the resulting offspring and identifying mice that secreted hFVIII in milk by RT-PCR and analysis of the milk for protein (paragraph bridging columns 1 and 2 of pg 263). Chen did not delete the B-domain of hFVIII.

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Thus, it was obvious to those of ordinary skill in the art at the time of filing to make a transgenic mouse encoding hFVIII as taught by Chen, wherein the hFVIII had a deletion in the B-domain as taught by Soukharev. Soukharev provides motivation on pg 241, lines 1-5. Those of skill would have a reasonable expectation of successfully improving the yield of FVIII as suggested by Soukharev because results in vitro improved the yield (pg 237, "Genetic engineering to improve the yield of recombinant

FVIII). Lubon provides further evidence that fragments of hFVIII could be made in a non-human transgenic animal (claim 1 of Lubon).

The phrase "recombinant spliced site, Ser 741 link to Leu 1643" is included because the metes and bounds of the structure claimed cannot be determined.

Claim 27 is included because "producing up to 50 mg" per liter encompasses expressing any amount up to 50 mg/l (µg/ml) and because Chen taught an average concentration of hFVIII of 20 µg/ml. The phrase "up to 50" µg/ml encompasses 20 µg/ml taught by Chen. Claim 27 is also included because Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "up to 50 µg/ml" as claimed.

The combined teachings of Chen and Soukharev taught making a transgenic mouse comprising a vector encoding B-domain deleted hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid signal peptide sequence. The combined teachings of Chen and Soukharev did not teach replacing the 19 amino acid a-LA signal peptide of SEQ ID NO: 13 with the 15 amino acid α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2).

However, DeBoer taught a nucleic acid construct comprising various nucleic acid elements for the optimization of producing recombinant protein in the milk of transgenic animals, said recombinant protein including FVIII (col. 7, line 12) including the alpha S1 casein secretion signal peptide (col. 7, lines 18-27). DeBoer also taught using the alpha-lactalbumin, whey acidic protein, beta-casein and alpha S1 casein (col. 2, line 53 to col. 3, line 5).

Thus, it was obvious to make a transgenic mouse encoding B-domain deleted hFVIII operably linked to the as taught by the combined teachings of Chen and Soukharev, wherein the a-lactalbumin signal peptide of SEQ ID NO: 13 was replaced with the α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2). One of ordinary skill in the art would have been motivated to use the α-S1 casein signal peptide instead of the α- lactalbumin signal peptide to increase secretion of hFVIII into the milk. Those of skill would have a reasonable expectation of successfully swapping signal peptides in view of the teachings of DeBoer. Lubon provides further evidence that signal peptides could be readily swapped to increase secretion into the milk of a non-human transgenic animal. Lubon states the "[i]mportant to the present invention are regulatory sequences that direct secretion of proteins into milk and/or other body fluids of the transgenic animal. In this regard, both homologous and heterologous regulatory sequences are useful in the invention. Generally, regulatory sequences known to direct the secretion of milk proteins, such as either signal peptides from milk proteins or the nascent target polypeptide, can be used..." (col. 6, lines 45-52).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

Applicants argue the prior art does not provide a reasonable expectation of success. Applicants' argument is not persuasive. Applicants' argument is unfounded. Furthermore, Chen and Soukharev both obtained functional expression of full length hFVIII in transgenics and B-domain deleted FVIII in vitro.

Applicants argue the second Declaration by Chen provides a Table comparing full-length FVIII and B-domain deleted FVIII expression in transgenics. Applicants argue the combination of elements described by Chen, Soukharev and DeBoer gave unexpected expression levels of FVIII. Applicants' arguments and the second Declaration by Chen remain not persuasive. Chen taught an average concentration of hFVIII of 20 µg/ml, which meets the limitation of "up to 50 mg" per liter as claimed (claim 27). Furthermore, Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which meets the limitation of "up to 50" µg/ml as claimed. The Table in the second declaration fails to take into account the increase in expression described by Soukharev when the B-domain is deleted and fails to account for using the bovine αS1 casein signal peptide described by DeBoer. Finally, the claims do not require expression of B-domain deleted FVIII beyond that expected from the combined teachings of Chen, Soukharev and DeBoer. The combination of elements described by Chen, Soukharev and DeBoer did not provide unexpected expression levels of FVIII when compared to claim 19 and meet the levels specifically set forth in claim 27.

Applicants argue the combination of elements described by Chen, Soukharev and DeBoer gave unexpected clotting activity of FVIII. The second Declaration by Chen provides Table 2 which states the activity of B-domain deleted FVIII in transgenics was 10-15% as compared to 5-10% for full-length FVIII described by Chen. Applicants conclude the increase in activity observed when the B-domain of FVIII was deleted was unexpected. Applicants' arguments remain not persuasive. Applicants' analysis fails to

compare the activity of transgenics claimed to the expected activity of transgenics made by the combined teachings of Chen, Soukharev and DeBoer. Applicants merely provide the expected activity of Chen alone, not the expected activity of the combined teachings of Chen, Soukharev and DeBoer. Furthermore, Soukharev cites Toole (PNAS, Aug. 1986, Vol. 83, pg 5939-5942) (see pg 237, col. 2, line 2) who taught activity was greater in B-domain deleted FVIII than wild-type (pg 5941, sentence bridging col. 1 and 2). Therefore, the increase in activity observed was expected. In the alternative, Soukharev also cites Pittman (Blood, 1993, Vol. 81, pg 2925-2935) (pg 237, col. 2, line 13) who taught activity was the same in B-domain deleted FVIII and wild-type. If so, the increase in activity observed was caused by the bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) (pg 5 of second declaration); however, only claims 22 and 23 require a bovine αS1-casein signal sequence and none of the claims require the S741-line to-L1643 recombinant splice site for the B-domain deletion. The bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) are essential to obtain the increase in FVIII activity observed by applicants. Applicants have not shown the increase in activity observed was unexpected as compared to the combined teachings of Chen, Soukharev and DeBoer or correlates properly to the claims as broadly written. Accordingly, applicants' arguments regarding unexpected FVIII activity are not persuasive.

Applicants argue the construct used by applicants was different than the one taught by the combined teachings of Chen, Soukharev and DeBoer. Applicants'

argument is not persuasive. The construct used in claim 19 is not different than the construct used by the combined teachings of Chen, Soukharev and DeBoer.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner